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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,146	05/03/2006	David R. Scholl	DHI-10857	8820

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MEDLEN & CARROLL, LLP
101 HOWARD STREET
SUITE 350
SAN FRANCISCO, CA 94105

EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,146	SCHOLL ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 11, 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,43-45,47,52-55 and 68* is/are pending in the application.

4a) Of the above claim(s) *44, 45, 55 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,43,47 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/3/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's amendments.

Claims 41, 43, 47 and 52-54 are examined on the merits.

Election/Restrictions

This application contains claims 44, 45, 55 and 68 drawn to an invention and species nonelected without traverse in the reply filed on April 30, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/699,936, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The limitations of claims 52-54

(protease inhibitor contained with cyclodextrin; cyclodextrin is Captisol; and protease inhibitor is…E64D) are not supported by the disclosure of '936. Therefore, their priority date is that of PCT/US04/36689, which was filed on November 3, 2004.

Response to Arguments

Applicant's arguments filed November 11, 2008 have been fully considered but they are not persuasive. See response below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(New Rejection Necessitated by Amendments) Claims 41, 43, 47 and 52-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 41 previously recited, "A method for detecting a virus that is not a plus-strand RNA virus in a sample, comprising:

a)providing: i) a sample; ii) cells susceptible to said virus that is not a plus-strand RNA virus; and iii) at least one protease inhibitor;

b) contacting said cells and said sample in the presence of said protease inhibitor to produce contacted cells, wherein replication of said virus that is not a plus-strand

RNA virus in said contacted cells is not reduced relative to replication of said virus that is not a plus-strand RNA virus in cells not contacted with said protease inhibitor, and wherein replication of a plus-strand RNA virus in said cells contacted with said protease inhibitor is reduced relative to replication of said plus-strand RNA virus in cells not contacted with said protease inhibitor." (This method is supported in the specification on page 6, abridging paragraph of lines 25-34 to page 7, lines 1 and 2; and page 7, lines 9-18).

Applicants have amended claim 41 to recite, "…b) contacting said cells and said sample in the presence of said protease inhibitor to produce contacted cells, wherein replication of said virus that is not a plus-strand RNA virus in said contacted cells is not reduced relative to replication of a coronavirus in said cells contacted with said protease inhibitor, wherein said coronavirus replication is at least 25% lower than said not a plus-strand RNA virus replication." (amendments underlined)

To support these amendments applicants point to page 98, lines 11 and 12 (see below),

Table 5. Number of Infected Foci In R-Mix Cell Cultures Contacted With a Respiratory Virus in the Presence of a Protease Inhibitor[1]

Virus	Control*	Actinonin			Glycyerrhizin			E64		
	0	40**	20	10	6.08	1.216	0.152	10	5	0.5
FluA	189 ± 012	118	122	171	163	175	218	176	179	174
FluB	455 ± 022	190	260	317	273	402	426	323	328	398
Adeno	863 ± 100	147	383	781	1061	938	766	865	868	904
RSV	116 ± 012	41	64	103	53	103	130	103	115	107
Para1	245 ± 018	160	191	222	295	233	268	207	243	251
Para2	243 ± 012	151	196	220	281	257	265	205	221	223
Para3	142 ± 014	75	104	115	138	149	138	107	99	127

[1] Concentration of protease inhibitors is shown in micrograms/ml, * mean of 6 samples; **Evidence of cell toxicity; R-Mix lot 960925.

The above results demonstrate that protease inhibitors are not inhibitory to infection by any of the seven exemplary viruses that are detected by Mv1Lu cells and/or R-Mix cells. This is in contrast to the inventors' data demonstrating inhibition in replication of human coronavirus 229E by the protease inhibitor E64.

page 102, lines 20-22,

Viral Induced Cellular Protein (VICP) Detection

After 16-18 hours incubation, remove vials from incubator, and aspirate the media. Add 0.5ml methanol to each vial, and let set at room temperature for 10 minutes. Then aspirate methanol, and add 0.5ml of sterile PBS to each vial. After aspirating the PBS rinse, add 0.2 ml of Chemicon Pan-Entero Blend mAb and incubate for 1 hour at 35-37°C. Aspirate the primary mAb solution and rinse with 1.0 ml of PBS. Aspirate the PBS, add 0.2 ml of DHI ELVIS Solution 3, and incubate for 1 hour at 35-37°C. Aspirate Solution 3, rinse coverslip in ddH_2O and place cell side down onto a drop of DHI Mounting fluid (placed on a glass slide). Examine for fluorescent green plaques by UV microscopy.

In an exemplary 16 hour bio-assay, the protease inhibitor E64d inhibited the replication of human coronavirus 229E by 100% at concentrations of 32ug/ml to 2ug/ml. 90% inhibition was obtained with E64D concentrations of 1ug/ml and 0.5ug/ml. This result was based on the percentage of fluorescent plaques observed in the drug treated vials as compared to the 0 drug control vials.

and page 17, lines 13-26.

> Unless defined otherwise in reference to the level of molecules and/or phenomena, the terms "reduce," "inhibit," "diminish," "suppress," "decrease," and grammatical equivalents when in reference to the level of any molecule (*e.g.*, nucleic acid sequence such as "gRNA," "sgRNA," amino acid sequence such as "Nucleocapsid," "Spike," "Matrix," "E protein," and "Replicase proteins," *etc.*), and/or phenomenon (*e.g.*, susceptibility, permissivity, infection with a microorganism, binding to a molecule, expression of a nucleic acid sequence, transcription of a nucleic acid sequence, enzyme activity, *etc.*) in a first sample relative to a second sample, mean that the quantity of molecule and/or phenomenon in the first sample is lower than in the second sample by the specified amount. In one embodiment, the reduction may be determined subjectively, for example when a patient refers to their subjective perception of disease symptoms, such as pain, difficulty in breathing, clarity of vision, nausea, tiredness, *etc.* In another embodiment, the quantity of molecule and/or phenomenon in the first sample is at least 10% lower than, at least 25% lower than, at least 50% lower than, at least 75% lower than, and/or at least 90% lower than the quantity of the same molecule and/or phenomenon in a second sample.

However, the specification does not support comparing the inhibitory effects on "not a plus-strand RNA virus" to that of coronavirus replication (i.e., "…relative to replication of a coronavirus…"), nor the limitation "…coronavirus replication is at least 25% lower than said not a plus-strand RNA virus replication". The specification only supports that comparison of cells contacted with or without protease inhibitors and the effects these inhibitors have on the replication of the same virus, not the comparison of a non-plus stranded RNA virus to a coronavirus.

Furthermore, page 98 (presented above) states that the data of Table 5 is in contrast to the data from testing E64 for any inhibitory affects against coronavirus 229E replication. However, the cells used in Table 5 and testing E64-229E inhibition are different as compared to the claimed method, which requires that the same "contacted

cells" be used when determining the relative replication of "not a plus-strand virus" to a coronavirus.

Moreover, lines 20-22 of page 102 do not support the claimed method or the new amendments. The presented data only establishes that at range of 0.5ug/ml to 32ug/ml E64D in MRC-5 cells can inhibit up to 100% viral infection.

Lastly, page 17 does not support the claim amendments since this section of the specification focuses on comparing the same molecule/phenomenon (not different viruses: i.e., non-plus stranded RNA viruses and coronaviruses) from a first sample and a second sample. In addition, page 17 lines 13-26 do not discuss comparing replication of viruses, but gene expression and molecular interactions. This paragraph also states that the first sample is "at least 10% lower, at least 25% lower..." than the second sample; conversely, the claimed method presently requires that the second sample (i.e., coronavirus) be at least 25% lower than the first sample (not a plus-strand virus).

Therefore the newly claimed method is not supported by the specification and the amendments constitute new matter.

Claim Objections

Claim 41 is objected to because of the following informalities: the claim recites, "…relative to replication of of a coronavirus…" and "…of a coronavirus virus in said cells…" Please amend the claim to recite, "…relative to replication of a coronavirus…" and "…of a coronavirus in said cells…" Appropriate correction is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stacy B Chen/
Primary Examiner, Art Unit 1648

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648